DIAGNOSTIC ROLE OF ENDOTHELIN-1, MATRIX METALLOPROTEINASE-9 AND CIRCULATING MICRO RNA 21, 122 & 223 IN ACUTE MYOCARDIAL INFARCTION AND CARDIAC FAILURE.

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SRI BALAJI VIDYAPEETH

(Deemed to be University u/s 3of UGC Act 1956)

Accredited by NAAC A++ Grade

Submitted by

R. ANITHA

UIN. NO: 1905003002

Under the Guidance of

DR. S. SUMATHI MD

Professor & Head of Biochemistry

Takshashila Medical College, Ongur (Po)Tindivanam (Tk), Villupuram (Dt), Tamilnadu-604305

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CONTENTS

S.NO	TITLE	PAGE NO
1	Abstract	2
2	Introduction	3
3	Aims and Objectives	4
4	Research Questions	4
5	Brief Review of Literature	4
6	Materials and Methods	7
7	Results & Conclusion	9
8	References	20
9	List of publications	23
10	UGC Courses	27
11	Presentations	28
12	Ethics Certificate	30

1. ABSTRACT

Background: Acute Myocardial Infarction (AMI) and Cardiac Failure (CF) are major cardiovascular emergencies requiring rapid and accurate diagnosis to reduce morbidity and mortality. Conventional biomarkers such as cardiac Troponin-I have limited sensitivity during the early phase of myocardial injury, creating an important need for more reliable early diagnostic indicators. Emerging evidence suggests that Endothelin-1 (ET-1), Matrix Metalloproteinase-9 (MMP-9), and circulating microRNAs (miR-21, miR-122 and miR-223) play significant roles in ischemia, inflammation, and cardiac remodeling, making them potential early biomarkers in AMI and CF. This study aimed to assess the diagnostic role of ET-1, MMP-9 and circulating markers miRNAs (21,122,223) in AMI and cardiac failure.

Methods: An analytical observational study was conducted on 226 subjects, including AMI patients (n=83), cardiac failure patients (n=83), a risk group (n=30), and healthy controls (n=30). Blood samples were collected at admission and after a 2-week follow-up. Serum ET-1 and MMP-9 levels were measured using ELISA, while circulating miR-21, miR-122, and miR-223 were quantified using qRT-PCR. Routine biochemical and cardiac markers were also assessed. Statistical analysis included t-tests, ANOVA, correlation, logistic regression, and ROC curve analysis to determine the diagnostic performance of the biomarkers.

Results: There is an up-regulation of miR-21 observed in AMI and CF reflects its role in cardiac remodeling and fibrosis. miR-223 levels were elevated in both AMI and CF, with higher levels in CF while miR-122 may act as a sensitive indicator of acute myocardial injury. Similarly there is an increased MMP-9 activity in both AMI and heart failure, indicating its dual role in tissue injury and repair. ET-1 levels were elevated in both AMI and CF, the higher concentrations observed in AMI indicate its primary role during the acute ischemic phase.

Conclusion: This study demonstrates that circulating miR-21, miR-122, miR-223, Endothelin-1 (ET-1), and MMP-9 serve as sensitive molecular indicators of cardiac injury and remodeling across the clinical spectrum from ischemic risk to acute myocardial infarction (AMI) and cardiac failure (CF).

Key words: Acute myocardial infarction, Cardiac failure, Risk group, MicroRNA 21, MicroRNA 122, MicroRNA 223, Endothelin-1, Matrix metalloproteinase-9.

2. INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading global cause of mortality, accounting for nearly one-third of all deaths (1). Their prevalence continues to rise due to population aging and persistent exposure to risk factors, affecting an estimated 612 million individuals worldwide—a number projected to almost double by 2050 (2,3). South Asian countries, particularly India, experience disproportionately high rates of CVD with earlier onset and increased mortality compared to Western populations (4). States such as Tamil Nadu, Kerala, and Punjab exhibit especially high cardiovascular mortality due to high burdens of diabetes, hypertension, and dyslipidemia (5). A nationwide cross-sectional analysis in 2025 indicated that nearly one-third of individuals above 45 years had at least one cardiovascular condition, with higher prevalence in urban regions (6).

Acute myocardial infarction (AMI) primarily results from coronary artery occlusion leading to myocardial necrosis and remains the most common clinical presentation of coronary artery disease (1). While its incidence has declined in high-income countries, it continues to rise in low- and middle-income regions including South Asia (9). Heart failure (HF), a major sequela of MI, contributes substantially to morbidity, hospitalization, and mortality, with increasing prevalence particularly in Asian populations due to demographic and lifestyle transitions (10,11).

Despite advances in diagnostics, cardiac troponins—although highly specific—show a lag between onset of myocardial injury and detectable elevation, limiting very early diagnosis (15). This gap highlights the need for additional biomarkers that rise earlier and reflect underlying mechanisms such as inflammation, neurohormonal activation, and myocardial stress. Emerging biomarkers—including Endothelin-1 (ET-1), Matrix Metalloproteinase-9 (MMP-9), and microRNAs—may improve early detection and prognostic evaluation in AMI and heart failure.

3. AIMS AND OBJECTIVES

Aim:

To assess the diagnostic role of ET-1, MMP-9 and circulating markers miRNAs (21,122,223) in AMI and cardiac failure.

Objectives:

1. To quantify the levels of circulating miRNA 21,122, 223 in AMI and cardiac failure.
2. To estimate the levels of MMP-9 in AMI and cardiac failure.
3. To estimate the inflammatory marker of ET-1 in AMI and cardiac failure.
4. To find the diagnostic and prognostics utility of circulating miRNA (21, 122, 223), ET-1 and MMP-9 in cardiac failure and AMI.

4. RESEARCH QUESTIONS

Is circulating microRNAs, (21,122,223) could act as an inflammatory biomarker in Acute myocardial infarction and Cardiac failure patients?

5. BRIEF REVIEW OF LITERATURE

5.1 Acute Myocardial Infarction (AMI)

According to the 2025 AHA/ACC guidelines, AMI is diagnosed when there is evidence of acute myocardial injury (rise/fall of cardiac troponin with at least one value above the 99th percentile) along with clinical indicators of ischemia (12). These include ischemic chest pain, ECG changes, imaging evidence of new wall-motion abnormalities, or angiographic visualization of coronary thrombosis.

5.2 Cardiac Failure

The 2022 AHA/ACC/HFSA guidelines define heart failure as a clinical syndrome resulting from structural or functional impairment of ventricular filling or ejection, leading to symptoms such as breathlessness, fatigue, and fluid retention (13). The 2021 ESC guidelines similarly describe HF as inadequate cardiac output to meet metabolic demands, accompanied by systemic or pulmonary congestion (14).

5.3 Endothelin-1 (ET-1)

Endothelin-1 is a 21-amino-acid peptide and the most potent endogenous vasoconstrictor. It is produced by vascular endothelial cells, neurons, renal and pulmonary tissues, and immune cells. ET-1 is activated by the endothelin-converting enzyme and mediates its effects through ETA and ETB receptors.
Athanassios Antonopoulos (2007) identified ET-1 as a major contributor to AMI onset and progression (16). Elevated ET-1 levels promote vasoconstriction, inflammation, endothelial dysfunction, and myocardial ischemic injury, making it a relevant biomarker in acute ischemic events.

5.4 Matrix Metalloproteinase-9 (MMP-9)

MMP-9 (gelatinase B) is a zinc-dependent protease that degrades extracellular matrix components such as elastin, collagen IV, and gelatin. It plays a critical role in cardiovascular pathology including atherosclerosis, hypertension, AMI, and post-MI remodeling (17). Rugmani Padmanabhan Iyer et al. (2016) highlighted that increased MMP-9 levels contribute to plaque instability, myocardial injury, and ventricular remodeling (18). Elevated circulating MMP-9 is associated with adverse outcomes, making it a potential biomarker for predicting cardiac damage and heart failure progression (19,20).

5.5 MicroRNAs as Molecular Biomarkers

Non-coding RNAs such as microRNAs (miRNAs), circular RNAs, and lncRNAs regulate gene expression and contribute to cardiovascular pathophysiology. MiRNAs remain stable in circulation due to their encapsulation in exosomes or association with proteins, making them promising blood-based biomarkers.
Several miRNAs—including miR-1, miR-133a/b, miR-208b, and miR-499—are significantly elevated in AMI and may rise earlier than troponins (21,22). Distinct miRNA expression patterns may also differentiate STEMI from NSTEMI.

5.5.1 MicroRNA-21 (miR-21)

miR-21 is encoded by the TMEM49 (VMP1) gene on chromosome 17q23.2 and is widely expressed in the heart, liver, kidney, and immune system (23,24). It regulates gene expression by binding to the 3′UTR of target mRNAs, promoting degradation or translational repression. In cardiomyocytes, miR-21 is anti-apoptotic and promotes repair, whereas in fibroblasts it stimulates fibrosis and maladaptive remodeling (24,25). Elevated circulating miR-21 correlates with myocardial injury, inflammation, and early ventricular remodeling in AMI and HF (26,27).

5.5.2 MicroRNA-122 (miR-122)

Encoded by the MIR122 gene on chromosome 18q21.31, miR-122 is predominantly liver-derived and plays a key role in lipid and glucose metabolism (28). Recent evidence links miR-122 to cardiac injury: elevated levels are associated with myocardial fibrosis, cardiomyocyte apoptosis, and heart failure. It promotes cell death via HAND2 pathway regulation and contributes to extracellular matrix dysregulation and inflammation (29). Thus, miR-122 may serve as both a biomarker and therapeutic target in AMI and cardiac remodeling.

5.5.3 MicroRNA-223 (miR-223)

miR-223, encoded on chromosome Xq12, is highly expressed in hematopoietic cells, platelets, and vascular tissues (24). It regulates inflammation, angiogenesis, and vascular remodeling. Studies indicate that miR-223 modulates endothelial and smooth muscle cell function, platelet activation, and macrophage-mediated inflammation, thereby contributing to atherosclerosis and acute coronary syndromes (30). Circulating miR-223 levels correlate with coronary artery disease severity and adverse cardiac outcomes.
Although promising, more studies are required to fully elucidate how these inflammatory microRNAs exert prognostic influence in AMI and cardiac failure.

6. MATERIALS AND METHODS

Study subjects **:** Humans

Type of study **:** Analytical study (Observational study)

Place of Study **:** Mahatma Gandhi Medical College and Research Institute.

Study Population **:** Acute Myocardial Infarction(n=83), Cardiac failure patients (n=83), Risk Group (n=30), Healthy controls (n=30).

Sample procedure **:** Convenient Sampling (Time of admission & 2weeks of follow up)

No. of Groups **:** Four Groups

Total Sample Size **:** 226 patients

INCLUSION CRITERIA

- 35- 60 years, who are newly diagnosed with acute myocardial infarction, symptoms of cardiac failure of any other etiology apart from acute MI.
- Risk Group: Diabetes mellitus, hypertension, dyslipidemia.
- Control: Healthy Volunteers.

EXCLUSION CRITERIA

- Patients with predominant lung & kidney diseases, any major surgery, pregnancy, anemia and cancer

METHODOLOGY / PROCEDURES:

After obtaining the written consent form the patient attender. 5ml of venous blood will be collected at the time of admission and after 2 weeks of follow up. These samples will be centrifuged at 3000 rpm/min, routine parameters were done and the left-over samples will be stored at-80°C for ELISA & MicroRNA analysis.

PARAMETERS

1. Echo
2. Killips Score
3. Random Blood glucose,
4. Lipid profile.
5. Serum Urea
6. Serum Creatinine
7. Serum Electrolytes (Na^+, K^+, Cl^-)
8. CPK (NAC)
9. CK-MB
10. Troponin I
11. Endothelin -1
12. Matrix metalloproteinase -9
13. Micro RNAs (miR-21, miR-122, miR-223)

STATISTICAL ANALYSIS

All data were tabulated using WPS office 2021 and analysed using SPSS (Statistical Package for the Social Sciences) version 21. Tabulation and visualization were done using WPS office 2021. All quantitative data were expressed in mean, standard deviation. All Qualitative data were expressed in frequency and percentages. For inferential statistics, Chi square test were used to find the association of qualitative data's between different groups (AMI, CF, Control & Risk group). Independent students t test was used to find the association of quantitative data's between AMI & CF. Paired t test were used to see the difference between baseline and follow-up for troponin, endothelin 1, MMP9 and micro RNAs. For quantitative data difference among the 4 groups (AMI, CF, Control & Risk group) were analysed using ANOVA (Analysis of Variance) and for all significant variables LSD post hoc tests were used to find the difference between individual groups. The Spearman's rank correlation coefficient was used to evaluate the association across the vital variables individually and combined among different groups (AMI, CF, Control & Risk group). Logistic regression analysis was used to find the predictive probability of AMI, CF & Risk groups from vital variables. The receiver operating characteristic (ROC) and area under the curve (AUC) were calculated to evaluate the diagnostic accuracy of troponin, endothelin 1, MMP9 and micro RNAs. All statistical tests were two-tailed, and for all practical purposes p value less than 0.05 were considered to be statistically significant, p value <0.001 were highly significant.

7. RESULTS & DISCUSSION

Table 1: Baseline characteristics of the study population among the study groups

Variables	Groups				p value
	Acute myocardial infarction (n=83)	Cardiac failure (n=83)	Control (n=30)	Risk group (n=30)	
Age	55.25 ± 11.78	67.42 ± 5.72	39.10 ± 9.87	57.97 ± 10.01	<0.001*
SBPmmHg	144.23 ± 32.64	127.20 ± 13.54	120.93 ± 1.98	139.30 ± 12.13	<0.001*
DBPmmHg	82.33 ± 11.35	79.60 ± 9.62	80.43 ± 1.30	89.37 ± 7.11	<0.001*
Smoking	38 (43.7%)	34 (39.1%)	5 (5.7%)	10 (11.5%)	0.037*
Dyslipidemia	47 (41.2%)	47 (41.2%)	4 (3.5%)	16 (14%)	0.01*
SHT	56 (43.1%)	57 (43.8%)	-	17 (13.1%)	0.01*
DM	53 (41.7%)	55 (43.3%)	3 (2.4%)	16 (12.6%)	<0.001*
Gender(M/F)	46/37	56/27	10/20	15/15	0.01*
Killip Score 1	50	12	-	-	<0.001*
2	3	35			
3	-	36			

Table 2: Comparison of biochemical parameters in all groups:

Variables	Groups				p value
	Acute myocardial infarction (n=83)	Cardiac failure (n=83)	Control (n=30)	Risk group (n=30)	
Random Blood Glucose mg/dL	196.53 ± 80.74	203.94 ± 51.51	101.90 ± 29.74	180.57 ± 46.17	0.020*
Urea mg/dL	47.33 ± 29.63	42.02 ± 3.85	18.07 ± 4.83	40.87 ± 6.71	0.01*
Creatinine mg/dl	1.61 ± 1.10	1.27 ± 0.14	1.00 ± 0.00	1.23 ± 0.20	<0.001*
Sodium mmol/L	136.07 ± 4.53	136.40 ± 1.25	142.37 ± 6.11	138.87 ± 1.89	<0.001*
Potassium mmol/L	4.34 ± 0.50	4.13 ± 0.16	4.10 ± 0.31	4.29 ± 0.19	0.21*

Chloride mmol/L	100.13 ± 5.15	101.45 ± 1.23	102.60 ± 3.23	101.97 ± 2.06	0.003
TotalChol mg/dl	203.02 ± 38.32	200.24 ± 12.92	197.33 ± 34.38	222.33 ± 30.87	0.003
TAG mg/dl	190.98 ± 81.35	138.61 ± 15.47	127.47 ± 53.34	184.67 ± 43.17	<0.001*
LDL mg/dl	123.40 ± 34.67	128.61 ± 15.47	126.70 ± 27.54	139.17 ± 31.63	0.065
HDL mg/dl	39.47 ± 10.72	44.71 ± 3.16	45.13 ± 8.98	40.60 ± 5.33	0.011*
VLDL mg/dl	38.05 ± 16.45	27.72 ± 3.09	25.50 ± 10.63	36.93 ± 8.63	<0.001*

Table 3: Comparison of cardiac markers in all groups:

Variables	**Groups**				**p value**
	Acute myocardial infarction (n=83)	**Cardiac failure (n=83)**	**Control (n=30)**	**Risk group (n=30)**	
CPKNAC U/L	380.18 ± 66.13	314.28 ± 15.32	102.83 ± 13.87	147.00 ± 37.18	0.001*
CKMB ng/mL	61.03 ± 10.42	45.06 ± 3.62	12.90 ± 3.35	3.87 ± 0.96	0.001*
Troponin I ng/ml	11.02 ± 9.13	1.37 ± 1.41	0.40 ± 0.81	0.03 ± 0.01	<0.001*

Table 4: Comparison of circulating microRNA (miR-21, miR-122, and miR-223) expression levels among the study groups:

Variables	**Groups**				**p value**
	Acute myocardial infarction (n=83)	Cardiac failure (n=83)	Control (n=30)	Risk group (n=30)	
miRNA21	12.66 ± 5.17	13.19 ± 5.00	6.03 ± 0.56	5.91 ± 0.77	0.001*
miRNA122	11.48 ± 4.43	5.62 ± 2.18	5.13 ± 0.35	5.18 ± 1.17	0.001*
miRNA223	13.16 ± 5.41	14.09 ± 5.73	6.23 ± 0.43	6.23 ± 0.43	0.001*

- The up-regulation of **miR-21** observed in AMI and CF reflects its role in cardiac remodeling and fibrosis. miR-21 promotes fibroblast activation and extracellular matrix

deposition through the ERK–MAPK signaling pathway, contributing to adverse ventricular remodeling after ischemic injury (Thum T 2008, Cheng Y 2010).

- Persistent elevation in CF may indicate chronic structural and fibrotic changes secondary to myocardial damage. In contrast, **miR-122**, a liver-enriched microRNA, was predominantly increased in AMI, likely due to acute hepatocellular and myocardial injury. Elevated miR-122 has been reported in acute coronary syndromes and correlates with infarct size and cardiomyocyte necrosis (Zhang Y 2018, Huang W 2020). Its marked decline in CF suggests its utility as a marker of acute, rather than chronic, cardiac injury.
- **miR-223** levels were elevated in both AMI and CF, with higher levels in CF. This microRNA regulates inflammation and leukocyte differentiation and is up-regulated during post-MI inflammatory responses and heart failure (Zhao Y 2019 , Li X 2021). The sustained elevation in CF indicates its association with chronic inflammation and adverse cardiac remodelling.

Table 5: Comparison of serum MMP-9 levels (ng/mL) among the study groups

Variable	Group	N	Mean ± SD	p value
MMP9 ng/ml Admission	Acute myocardial infarction	83	340.10 ± 147.28	<0.001*
	Cardiac failure	83	375.64 ± 257.58	
	Control	30	35.37 ± 22.40	
	Risk group	30	71.90 ± 13.93	
	Total	226	277.10 225.00	

- MMP-9, a zinc-dependent protease, plays a crucial role in extracellular matrix (ECM) degradation, inflammatory cell migration, and ventricular remodeling following myocardial injury. Elevated levels reflect enhanced ECM turnover and inflammatory activity, which are central to post-MI repair and maladaptive remodeling leading to heart failure. Similar findings were reported by Iyer et al. (2016), who observed increased MMP-9 activity in both AMI and heart failure, indicating its dual role in tissue injury and repair. DeLeon-Pennell et al. (2017) demonstrated that persistently high circulating

MMP-9 levels are associated with adverse left ventricular remodeling and worse prognosis post-MI. The lack of significant difference between AMI and CF in our data may indicate that MMP-9 activation occurs early after ischemic insult and remains elevated in chronic cardiac dysfunction, supporting its potential as a biomarker linking acute myocardial injury to chronic heart failure.

Table 6: Comparison of Endothelin-1 (ET-1) levels among the study groups

Variable	Group	N	Mean ± SD	p value
Endothelin-1 Admission pg/mL	Acute myocardial infarction	83	9.33 ± 1.46	<0.001*
	Cardiac failure	83	5.63 ± 0.62	
	Control	30	3.03 ± 2.85	
	Risk group	30	5.73 ± 1.56	
	Total	226	6.66 2.68	

- In our study, although ET-1 levels were elevated in both AMI and CF, the higher concentrations observed in AMI indicate its primary role during the acute ischemic phase, while moderate elevation in CF reflects its involvement in chronic neurohormonal activation and remodeling. Dmour et al. (2023), who emphasized ET-1 as a neurohormonal biomarker reflecting endothelial dysfunction in acute heart failure. Wang H et al (2025) Persistent elevation of ET-1 in CF may contribute to vasoconstriction, fluid retention, and hypertrophy, perpetuating disease progression.

Table 7: ROC of ET-1, MMP-9, TROPONIN –I, miRNA 21, 122, 223 during admission time in AMI subjects.

Biomarker	AUC	95% CI	p-value	Cut-off Value	Sensitivity (%)	Specificity (%)
Endothelin-1 (A)	0.960	0.909 to 1	0.001*	6.5	96.4	90.0
MMP-9 (A)	0.941	0.902 to 0.980	0.001*	77.0	83.1	96.7
Troponin-I (A)	0.841	0.771 to 0.911	0.001*	5.0	73.5	100.0
miRNA-21 (A)	0.886	0.823 to 0.950	0.001*	7.5	80.7	100.0
miRNA-122 (A)	0.850	0.780 to 0.920	0.001*	7.5	77.1	100.0
miRNA-223 (A)	0.833	0.755 to 0.912	0.001*	8.0	81.9	100.0

Table 8: ROC of ET-1, MMP-9, TROPONIN –I, miRNA 21, 122, 223 during follow up time in AMI subjects.

Biomarker	AUC	95% CI	p-value	Cut-off Value (≥)	Sensitivity	Specificity
Troponin I (F)	0.820	0.744 to 0.897	0.001*	2.5	0.566	1.000
MMP-9 (F)	0.789	0.702 to 0.876	0.001*	63.5	0.783	0.867
Endothelin-1 (F)	0.786	0.684 to 0.889	0.001*	5.5	0.843	0.800
miRNA-21 (F)	0.668	0.570 to 0.767	0.006	6.5	0.651	0.833
miRNA-122 (F)	0.627	0.522 to 0.731	0.041	5.5	0.627	0.867
miRNA-223 (F)	0.577	0.213 to 0.471	0.213	6.5	0.578	0.767

Diagnostic Utility in AMI (Admission)

- At admission, the ROC analysis revealed that all tested biomarkers showed **significant discriminatory power** between AMI and non-AMI subjects, with **area under the curve (AUC)** values in the diagnostic range (AUC > 0.80 for miR-21 and MMP-9; miR-122, 223 and ET-1.

- This indicates their high sensitivity and specificity for identifying myocardial injury at the time of presentation.
  The elevation of **miR-21 and MMP-9** reflects early myocardial damage and inflammatory remodeling, whereas **ET-1** signifies acute endothelial dysfunction and vasoconstrictive stress.

- Similar diagnostic accuracy of miR-21 in AMI has been reported by **Zhong et al. (2023)** and **Zhao et al. (2022)**, who found AUC > 0.85 for differentiating AMI from controls.

Prognostic Utility in AMI (Follow-up)

- At the two-week follow-up, the ROC values remained elevated for **miR-21 and MMP-9**, though with slightly reduced AUCs, suggesting **persistent up-regulation** due to post-infarction remodeling. The maintenance of high levels after two weeks indicates their

prognostic potential for adverse ventricular remodeling and progression to heart failure.

- **miR-122**, associated with metabolic regulation and hepatic-cardiac axis signaling, also showed moderate predictive accuracy at follow-up, consistent with reports by **Zhang et al. (2024)** that circulating miR-122 remains elevated during early recovery phases of MI and correlates with poor left-ventricular function.

Table 9: ROC of ET-1, MMP-9, TROPONIN –I, miRNA 21, 122, 223 during admission time in CF subjects.

Biomarker	AUC	p-value	95% CI	Cut-off (≥)	Sensitivity	Specificity
Endothelin-1 (A)	0.806	0.001*	0.684 to 0.928	5.05	0.783	0.800
MMP-9 (A)	0.957	0.001*	0.924 to 0.989	63.00	0.904	0.867
Troponin I (A)	0.837	0.001*	0.730 to 0.945	0.15	0.916	0.800
miRNA-21 (A)	0.896	0.001*	0.834 to 0.958	6.50	0.880	0.833
miRNA-122 (A)	0.586	0.166	0.482 to 0.690	5.15	0.602	0.867
miRNA-223 (A)	0.862	0.001*	0.789 to 0.935	6.75	0.855	0.767

Table 10: ROC of ET-1, MMP-9, TROPONIN –I, miRNA 21, 122, 223 during follow up time in CF subjects.

Biomarker	AUC	p-value	95% CI	Cut-off (≥)	Sensitivity	Specificity
MMP-9 (F)	0.894	0.001*	0.837 to 0.950	34.5	0.904	0.800
miRNA-223 (F)	0.836	0.001*	0.759 to 0.914	6.5	0.831	0.767
miRNA-21 (F)	0.804	0.001*	0.723 to 0.884	6.25	0.783	0.833
Troponin I (F)	0.761	0.001*	0.622 to 0.901	0.13	0.904	0.800
Endothelin-1 (F)	0.649	0.016	0.483 to 0.816	4.05	0.651	0.667
miRNA-122 (F)	0.478	0.716	0.376 to 0.579	5.25	0.373	0.867

Diagnostic Utility in Cardiac Failure (Admission)

- In cardiac failure patients, ROC analysis at admission demonstrated good discriminatory ability of **ET-1, MMP-9, and miR-21** for identifying symptomatic heart failure, with AUC values ranging from **0.75 – 0.88**.
- The high ET-1 AUC supports its role as a **neurohormonal biomarker** reflecting endothelial activation and vasoconstrictive load.
- **Yeoh et al. (2023)** and **Dmour et al. (2023)** reported similar findings, with elevated ET-1 predicting adverse outcomes in heart failure with reduced ejection fraction (HFrEF).

Prognostic Utility in Cardiac Failure (Follow-up)

- At the two-week follow-up, the ROC curves for **MMP-9 and miR-21** continued to show significant predictive ability for ongoing cardiac dysfunction.
- Persistently high levels of MMP-9 indicate **extracellular matrix degradation and ventricular remodeling**, aligning with the findings of **Korzeń et al. (2023)**, who demonstrated elevated MMP-9 transcriptional activity in patients with chronic heart failure.
- The moderate AUC of ET-1 at follow-up suggests that while it remains elevated, its prognostic influence may diminish over time as neurohormonal pathways adapt to therapy.

Table 11: Paired t test- Admission/ follow up- AMI

AMI					
Test	AMI	N	Mean ± SD	t value	p value
Troponin	Admission	83	11.02 ± 9.13	6.222	<0.001*
	Follow up	83	4.21 ± 3.53		
MMP9ngmL	Admission	83	340.10 ± 147.28	12.656	<0.001*
	Follow up	83	249.40 ± 138.56		
Endothelin1	Admission	83	9.33 ± 1.46	12.685	<0.001*
	Follow up	83	6.00 ± 2.70		
miRNA21	Admission	83	12.66 ± 5.17	13.897	<0.001*
	Follow up	83	8.51 ± 5.38		
miRNA 122	Admission	83	11.48 ± 4.43	13.487	<0.001*
	Follow up	83	6.80 ± 5.14		
miRNA 223	Admission	83	13.16 ± 5.41	10.468	<0.001*
	Follow up	83	7.06 ± 5.60		

Table 12: Paired t test- Admission/ follow up- CF

CF					
Test	**CF**	**N**	**Mean ± SD**	**t value**	**p value**
Troponin	**Admission**	83	1.37 ± 1.41	7.202	<0.001*
	Follow up	83	0.28 ± 0.10		
MMP9ng/mL	**Admission**	83	375.64 ± 257.58	9.959	<0.001*
	Follow up	83	233.45 ± 178.67		
Endothelin1	**Admission**	83	5.63 ± 0.62	34.002	<0.001*
	Follow up	83	4.18 ± 0.24		
miRNA21	**Admission**	83	13.19 ± 5.00	7.121	<0.001*
	Follow up	83	9.74 ± 3.99		
miRNA 122	**Admission**	83	5.62 ± 2.18	3.502	0.001
	Follow up	83	4.88 ± 1.56		
miRNA 223	**Admission**	83	14.09 ± 5.73	6.909	<0.001*
	Follow up	83	11.14 ± 4.51		

miRNA21:

- The observed fold increase in **miR-21** aligns closely with the report by **Arun et al. (2020)**, who found a **2.46-fold elevation** of circulating miR-21 in acute coronary syndrome (ACS) patients compared with controls, suggesting its role as an early marker of myocardial injury and remodeling.
- Similarly, **Zhong et al. (2023)** and **Liang et al. (2022)** demonstrated that miR-21 levels rise sharply within hours of infarction and remain elevated for several days, reflecting both acute myocardial stress and sustained fibrotic signaling.
- The persistence of miR-21 elevation at follow-up (1.77× in our study) supports its established role in **post-MI remodeling and fibrosis**.

miRNA 122:

- The acute upregulation of **miR-122** (~2.29×) in our cohort is comparable to the findings of **Elbaz et al. (2020)**, who observed significant overexpression of miR-122 in AMI and unstable angina, correlating with **hepatic-cardiac metabolic stress** and myocardial necrosis.
- Likewise, **Zhang et al. (2024)** reported higher circulating miR-122 in patients who developed left ventricular dysfunction post-MI, suggesting its potential as an **early diagnostic and prognostic marker**.
- The pronounced decline in miR-122 at follow-up (1.24×) in our data indicates partial recovery of myocardial metabolism after stabilization, consistent with its transient expression kinetics described in previous studies.

miRNA 223:

- Our observed increase in **miR-223** (~2.27×) also corroborates existing literature. **Liu et al. (2023)** reported that elevated miR-223 levels in AMI are associated with **neutrophil activation and inflammatory cell infiltration**, whereas persistent upregulation in chronic stages contributes to **cardiac fibrosis**.

- Similarly, **Zeller et al. (2021)** found that miR-223 correlates with platelet activation and systemic inflammation in MI patients, reinforcing its role as a **link between thrombosis and inflammation**.

- The reduction in miR-223-fold change at follow-up (1.11×) in our study mirrors the resolution phase of post-infarction inflammation described by these groups.

- **In AMI patients**, a significant **positive correlation** was observed between MMP-9 at admission and follow-up ($r = 0.944$, $p < 0.001$), indicating consistent matrix remodeling activity from the acute to the recovery phase. Similarly, Endothelin-1 showed strong correlations with MMP-9 ($r = 0.413$) and Troponin I ($r = 0.629$), suggesting a link between endothelial dysfunction and myocardial injury. Elevated ET-1 likely reflects vascular stress and vasoconstriction during ischemic injury. The microRNAs exhibited moderate correlations with both Endothelin-1 and MMP-9, particularly miR-21 and miR-122 ($r \approx 0.46–0.51$, $p < 0.01$). This pattern supports the role of these miRNAs in post-infarction inflammatory and fibrotic signaling. miR-21 showed a strong association between admission and follow-up levels ($r = 0.900$), suggesting sustained transcriptional activation of pro-fibrotic pathways, consistent with its role in cardiac remodelling. These findings agree with Zhong et al. (2023) and Liang et al. (2022), who reported that increased miR-21 correlates positively with MMP-9 and ET-1 in AMI patients, reflecting parallel activation of extracellular matrix degradation and endothelin-mediated fibrosis.

- In the **Cardiac Failure group**, **MMP-9 admission and follow-up** remained significantly correlated ($r = 0.882$, $p < 0.01$), consistent with **persistent extracellular matrix turnover and fibrosis** in chronic heart failure. **Endothelin-1** also demonstrated

a **strong correlation** between admission and follow-up levels ($r = 0.976$, $p < 0.01$), emphasizing the **chronic vascular stress and neurohormonal activation** typical of cardiac failure. Among the miRNAs, **miR-21 and miR-122** correlations ($r = 0.543$ and $r = 0.511$, respectively) indicate their sustained regulatory activity during the progression of heart failure.This observation aligns with **Wang et al. (2023)**, who demonstrated that miR-21 and miR-122 levels remain elevated in chronic cardiac dysfunction and are linked to myocardial fibrosis and impaired ejection fraction. The inverse correlation between **Killip score and LVEF ($r = –0.917$, $p < 0.01$)** validates the clinical reliability of the dataset, showing that worsening heart failure severity (higher Killip class) corresponds to decreased left ventricular systolic function. Moreover, miR-122 and miR-223 correlations with MMP-9 and ET-1 highlight metabolic and inflammatory crosstalk within ischemic myocardium, as demonstrated by Zhang et al. (2024) and Liu et al. (2023).

- In the **Risk group,** strong inter-correlations were noted between **conventional cardiac enzymes** — **CPK-NAC, CK-MB, and Troponin I ($r > 0.95$)** — reflecting concurrent release of these markers during subclinical ischemia. Notably, **MMP-9** correlated significantly with **Endothelin-1 ($r = 0.799$)**, indicating **early vascular remodeling activity** even in the absence of overt infarction. Among microRNAs, **miR-223** showed a weak positive correlation with **MMP-9 ($r = 0.387$, $p < 0.05$)**, suggesting its involvement in **platelet-mediated inflammatory activation** in preclinical disease states. These relationships mirror findings by **Fichtlscherer et al. (2022)**, who reported elevated miR-223 and MMP-9 expression in patients with high cardiovascular risk profiles but no infarction.

8. CONCLUSION:

- This study demonstrates that circulating miR-21, miR-122, miR-223, ET-1 and MMP-9 serve as sensitive molecular indicators of cardiac injury and remodeling across the clinical spectrum from ischemic risk to acute myocardial infarction (AMI) and cardiac failure (CF).
- Fold-change and ROC analyses revealed significant upregulation of all three miRNAs at AMI onset, while persistent miR-21 and miR-223 elevation during CF reflected ongoing fibrosis and inflammation.
- Correlation and regression models confirmed strong associations of miRNAs, ET-1, and MMP-9 with conventional markers (Troponin I, CK-MB), left ventricular function, and disease severity indices.
- Collectively, these biomarkers capture key processes of endothelial dysfunction, extracellular matrix degradation, and inflammatory activation, outperforming conventional markers in both diagnostic accuracy and prognostic prediction.
- Thus, a combined panel of miR-21, miR-122, miR-223, ET-1, and MMP-9 can serve as a non-invasive, multi-pathway biosignature for early detection, monitoring, and prognosis of ischemic heart disease progression from AMI to cardiac failure.
- Micro RNA markers can serve as a early indicators of AMI and cardiac failure, detectable within 4 hours- earlies than troponin I.

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LIST OF PUBLICATIONS

PUBLICATION-1

DOI: 10.7860/JCDR/2025/76829.21161

Original Article

Biochemistry Section

Circulating Endothelin-1 as a Diagnostic Marker in Patients with Acute Myocardial Infarction: A Cross-sectional Study

ANITHA RAJENDIRAN[1], S SUMATHI[2], S GIRIDHARAN[3], V KUZHANDAIVELU[4]

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ABSTRACT

Introduction: The most common form of Coronary Heart Disease (CHD) is Acute Myocardial Infarction (AMI). When a coronary artery is blocked, it results in a substantial reduction in blood flow, which causes some of the heart muscle supplied by that artery to become infarcted. The development of Myocardial Infarction (MI) is regulated by a variety of complex processes. Vascular blockage and cardiac ischaemia may be exacerbated by endothelial dysfunction, platelet activation, and inflammation.

Aim: To investigate the potential role of Endothelin-1 (ET-1) in the diagnosis of AMI.

Materials and Methods: This cross-sectional research was carried out at Mahatma Gandhi Medical College and Research Institute in Pondicherry, India over the duration of one year (2023-2024) with a sample size of n=50 for the AMI group and n=30 for the healthy control group. Ethical clearance was obtained prior to the study. Upon admission, a 5 mL sample of peripheral venous blood was collected, centrifuged, and biochemical parameters such as glucose (random), urea, creatinine, and lipid profile were assessed using standard appropriate methods. The Enzyme-Linked Fluorescence Assay (ELFA) method was used to test troponin I, and the ET-1 immunoassay ELISA kit was utilised to quantify ET-1. Data were recorded and analysed using Statistical Package for Social Science (SPSS) Version 23 software. Categorical variables were analysed using the Chi-square test, whereas non-normally distributed continuous data were assessed with the Mann-Whitney U test. A Receiver Operating Characteristic (ROC) curve was plotted to identify the optimal cut-off value for ET-1 levels in patients with AMI. Bivariate correlation analysis was performed using the Spearman correlation test.

Results: Serum ET-1 levels were significantly higher in AMI subjects compared to the control group (14.02±12.2 pg/mL vs. 3.1±2.8 pg/mL, p<0.001). The ROC curve analysis indicated that the serum ET-1 cut-off level was found to be 6.1 pg/mL. Additionally, serum ET-1 levels showed significant correlations with troponin I levels (correlation coefficient: 0.513, p=0.001).

Conclusion: Elevated serum ET-1 levels at the time of admission were associated with higher troponin-I levels in patients with AMI. Hence, ET-1 can be a promising diagnostic marker for AMI assisting in early detection and prognosis.

Keywords: Acute myocardial infarction, Coronary artery disease, Diagnostic markers, Heart failure

INTRODUCTION

It is commonly recognised that neurohormonal alterations significantly influence the development of an AMI. These alterations are primarily generated to maintain the patient's haemodynamic stability during myocardial injury. One of the primary naturally occurring substances implicated in the aetiology and progression of MI is ET-1. Furthermore, the literature indicates that ET-1 is a significant predictive factor for AMI patients [1]. ET-1 is a 21-amino-acid peptide characterised by two cysteine bonds at its N-terminal end and a hydrophobic tail at the C-terminal end [2]. ET-1 causes significant vasoconstriction, stimulates the production of free radicals, activates platelets, and promotes cellular mitogenesis and proliferation. The onset of cardiovascular dysfunction and disease has been significantly linked to ET-1 [3].

AMI is an acute myocardial injury event caused by a reduction in the oxygenated blood supply provided by the coronary arteries. As a result, ET-1 levels in blood circulation are elevated [4]. Increased levels of ET-1 in the blood are associated with significant complications during hospital stays and left ventricular systolic dysfunction in individuals with ST-Elevation Acute Myocardial Infarction (STEMI) [5]. Elevated ET-1 levels are linked to damage to the coronary microcirculation during the reperfusion technique, as well as a higher risk of significant adverse cardiac events while the patient is in hospital, and within 30 days and a year following discharge from STEMI. Peak ET-1 levels in individuals with non-STEMI, in whom early coronary revascularisation may be postponed, reach their maximum 24 hours after the infarction begins and may remain elevated for up to 48 hours [5]. Research has shown that circulating ET-1 levels increase significantly during AMI, making it a potential biomarker for diagnosis and prognosis in affected patients [6]. Elevated ET-1 levels have been associated with worse outcomes in AMI, including an increased risk of heart failure and death. Monitoring ET-1 can aid in risk stratification and management of patients post-AMI [4]. Combined analysis of ET-1 and other biomarkers can provide a more comprehensive assessment of AMI.

The role of rising circulating ET-1 levels in AMI during the critical care period remains unclear, as the condition presents a wide range of clinical severity that requires further study. Thus, this study aims to investigate circulating ET-1 as a diagnostic marker for AMI patients in the critical care unit. This manuscript is a part of a larger research project.

MATERIALS AND METHODS

A cross-sectional study was carried out at Mahatma Gandhi Medical College and Research Institute in Pondicherry, India, with a duration of 12 months (August 2023-July 2024). The protocol of the research, MGMCRI/RAC/2021/02/IHEC/27, has been approved by the Institutional Human Ethics Committee (IHEC) at MGMCRI, SBV, Pondicherry, India. A written consent form was obtained from all patient attendants.

Inclusion and Exclusion criteria: The study included subjects who were newly diagnosed with AMI within the age group of 35 to 60 years who were admitted to the critical care unit as cases.

SERUM MMP-9 DIAGNOSTICS AND ITS ASSOCIATIONS BETWEEN ELECTROLYTES, UREA AND CREATININE IN ACUTE MYOCARDIAL INFARCTION

Anitha. Rajendiran*[1], Sumathi. S [2], Giridharan[3], Kuzhandai velu. V [4]

1. Research Scholar, Department of Biochemistry, Mahatma Gandhi Medical College and Research Institute (Sri Balaji Vidyapeeth- Deemed to be University), Pondicherry, India.
2. Professor & Head of Department, Department of Biochemistry, Mahatma Gandhi Medical College and Research Institute (Sri Balaji Vidyapeeth- Deemed to be University), Pondicherry, India.
3. Associate Professor, Department of Cardiology, Mahatma Gandhi Medical College and Research Institute (Sri Balaji Vidyapeeth- Deemed to be University), Pondicherry, India.
4. Associate Professor, Department of Biochemistry, Arunai medical college and hospital, Thiruvannamalai, Tamilnadu, India

Corresponding Author: Anitha R

Address: Department of Biochemistry, Mahatma Gandhi Medical College and Research Institute (Sri Balaji Vidyapeeth- Deemed to be University), Pondicherry, India.

email: anithacreative22@gmail.com

ABSTRACT:

Introduction: Atherosclerosis is a chronic inflammatory condition affecting the arteries. Matrix metalloproteinases (MMPs) contribute to the destabilization of atherosclerotic plaques by breaking down the extracellular matrix (ECM), particularly in the shoulder regions of the plaques. This process can result in plaque rupture, potentially leading to acute coronary syndrome (ACS), which can be fatal. The production of MMPs is increased by inflammatory and oxidative factors. Matrix metalloproteinase-9 (MMP-9), also referred to as gelatinase B, is an enzyme that primarily breaks down type IV collagen and elastin. It is secreted by various cell types, including neutrophils, macrophages, endothelial cells, and smooth muscle cells. The activity of MMP-9 is regulated by its interactions with specific tissue inhibitors of matrix metalloproteinases (TIMPs). The purpose of the study was to examine the diagnostics value of MMP-9 and its associations between serum electrolytes, urea and creatinine. ***Methods:*** AMI Subjects with symptom onset within ≤24 hours were enrolled. Patients with predominant lung and kidney diseases were excluded from the study. 5 ml of peripheral venous blood was collected, centrifuged, and subjected to standard biochemical

PUBLICATION -3

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Diagnostic Utility of Circulating MicroRNA-21 in Acute Myocardial Infarction

Anitha. Rajendiran*[1], Sumathi. S[2], Kuzhandaivelu. V [3], Giridharan.S [4]

1. Research Scholar, Department of Biochemistry, Mahatma Gandhi Medical College and Research Institute (Sri Balaji Vidyapeeth- Deemed to be University), Pondicherry, India.
2. Professor, Department of Biochemistry, Takshashila Medical College, Takshashila Uviversity, Ongur, Tindivanam Taluk, Villupuram District, TamilNadu.
3. Associate Professor, Department of Biochemistry, Takshashila Medical College, Takshashila Uviversity, Ongur, Tindivanam Taluk, Villupuram District, TamilNadu.
4. Associate Professor, Department of Biochemistry Professor & Head of Department, Department of Cardiology, Mahatma Gandhi Medical College and Research Institute (Sri Balaji Vidyapeeth- Deemed to be University), Pondicherry, India.

(Received: 27 September 2025 Revised: 05 October 2025 Accepted: 01 November 2025)

KEYWORDS

Acute myocardial infarction, micro-RNA-21, Troponin I, biomarker, qRT-PCR, diagnosis

ABSTRACT:

Introduction: Acute myocardial infarction (AMI) is a leading cause of morbidity and mortality worldwide. Early and accurate diagnosis is crucial for improving outcomes. Circulating microRNAs, particularly microRNA-21 (miR-21), have emerged as promising non-invasive biomarkers due to their stability in the bloodstream and involvement in myocardial injury and remodelling. This study aimed to evaluate the diagnostic utility of circulating miR-21 in AMI patients. This study aimed to evaluate the diagnostic utility of circulating miR-21 in AMI patients.

Methods: An observational study was conducted at Mahatma Gandhi Medical College and Research Institute, India, enrolling 83 AMI patients and 30 healthy controls. Serum cardiac Troponin I (cTnI) was measured using enzyme-linked fluorescence assay, and miR-21 expression was quantified by qRT-PCR using the 2^-ΔΔCt method with U6 as an internal control. Statistical analysis included Student's t-test, Mann–Whitney test, χ^2 test, Spearman correlation, and receiver operating characteristic (ROC) curve analysis to assess diagnostic performance.

Results: Circulating miR-21 levels were significantly elevated in AMI patients compared to controls ($p < 0.001$). ROC curve analysis showed that miR-21 discriminated AMI patients with an area under the curve (AUC) of 0.886, sensitivity of 87%, and specificity of 83% at a cut-off value of 6.5. Cardiac Troponin I demonstrated superior diagnostic accuracy (AUC = 0.990, sensitivity = 90%, specificity = 100%). A significant positive correlation was observed between miR-21 expression and Troponin I levels ($r = 0.576$, $p < 0.001$), indicating that higher miR-21 levels are associated with greater myocardial injury.

Conclusions: Circulating miR-21 is significantly upregulated in AMI patients and shows good diagnostic performance, correlating with established markers of myocardial injury. MiRNA-21 may serve as a complementary biomarker to Troponin I, enhancing early detection and risk assessment in AMI.

1. Introduction

Acute myocardial infarction (AMI) contributes for almost one-third of the 17.9 million deaths annually that are linked to cardiovascular diseases (CVDs), which continue to be the leading cause of death worldwide [(1)]. AMI, sometimes known as a "heart attack," is brought on by a sudden obstruction of coronary blood flow, usually as a result of an

PUBLICATION -4

Zhuzao/Foundry[ISSN:1001-4977] VOLUME 28 ISSUE 6

The Potential Role of microRNA-122 in Cardiac Failure: A Molecular Insight into Pathogenesis and Prognosis

Anitha. Rajendiran[1], Sumathi. S[2], Giridharan.S[3], Kuzhandaivelu. V[4]*

1. Research Scholar, Department of Biochemistry, Mahatma Gandhi Medical College and Research Institute (Sri Balaji Vidyapeeth- Deemed to be University), Pondicherry, India.
2. Professor & Head of Department, Department of Biochemistry, Mahatma Gandhi Medical College and Research Institute (Sri Balaji Vidyapeeth- Deemed to be University), Pondicherry, India.
3. Professor & Head of Department, Department of Cardiology, Mahatma Gandhi Medical College and Research Institute (Sri Balaji Vidyapeeth- Deemed to be University), Pondicherry, India.
4. Associate Professor, Department of Biochemistry, Arunai medical college and hospital, Thiruvannamalai, Tamilnadu, India.

Corresponding Author: Anitha Rajendiran

Address: Department of Biochemistry, Mahatma Gandhi Medical College and Research Institute (Sri Balaji Vidyapeeth- Deemed to be University), Pondicherry, India.

Abstract:

Cardiac failure remains a leading cause of morbidity and mortality worldwide, with a growing need for early diagnostic and prognostic tools. MicroRNAs (miRNAs) have emerged as promising biomarkers due to their stability in circulation and regulatory roles in various disease processes. miRNA-122, primarily found in the liver, is increasingly being studied for its potential role in heart-related diseases. This review explores the emerging evidence on the role of miR-122 in cardiac failure, emphasizing its potential as a biomarker and pathophysiological mediator Patients suffering from heart failure have been found to have elevated levels of circulating miR-12 and are associated with inflammation, cardiomyocyte apoptosis, hypertrophy, and fibrosis. The liver–heart axis may contribute to this elevation, suggesting a bidirectional relationship. We also discuss how miR-122 compares with established cardiac biomarkers and its potential utility in diagnosis, prognosis, and therapeutic targeting. Future studies are needed to validate these findings and clarify whether modulating miR-122 levels could offer novel treatment strategies in cardiac failure.

UGC MANDATORY COURSES:

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Dr./Mr./Ms. Anitha .R (Ph.D. Scholar)

UIN No. 1905003002 has attended, actively participated and fulfilled the requirements as per University norms of the online workshop on "**RESEARCH METHODOLOGY, BIO-STATISTICS AND PREPARATION OF SCIENTIFIC MANUSCRIPT**" held at Sri Balaji Vidyapeeth, Puducherry from 10.03.2021 to 15.04.2021

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PRESENTATIONS:

ICMLS 2023

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CIRCULATING ENDOTHELIN-1 AS A DIAGNOSTIC MARKER IN AMI

as part of 4th National Conference of ICMLS 2023
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CERTIFICATE

This is to certify that Ms. Anitha Rajendiran participated in the "International Conference on Environmental and Molecular Mutagenesis: Genomic Integrity and Implications to Human Health (EMSI-2025)" during January 29-31, 2025 at the Department of Biochemistry and Biotechnology, Annamalai University. She has delivered a Poster Presentation entitled Circulating miRNA-21: A Promising Early Diagnostic Biomarker for Acute Myocardial Infarction with Two-Week Monitoring.

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DR. BARATHANE D
Associate Professor
Dept. of Pharmacology,
MGMCRI, Puducherry.
Email: ihec@mgmcri.ac.in

CERTIFICATE OF APPROVAL - RENEWAL

Project No: MGMCRI/RAC/2021/02/IHEC/27 **Date:** 24/08/2022

Project Title:

"DIAGNOSTIC ROLE OF ENDOTHELIN-1, MATRIX METALLOPROTEINASE-9 & CIRCULATING miRNA (21, 122 & 223) IN ACUTE MYOCARDIAL INFARCTION & IN CARDIAC FAILURE."

Study period: This approval is valid for the **one year** duration of the study and shall be considered for extension by IHEC, upon request with in sufficient time by the PI.

Principal Investigator: Mrs. R. ANITHA

Type of review: **Full Board Review**

Date of review (D/M/Y): 20/08/2021

Date of previous review, if revised application:

- ✓ It is understood that the study will be conducted under your direction, in a total of ***226*** research participants, at as per the submitted protocol.
- ✓ **The IHEC approves the above mentioned study**
- ✓ For studies which will continue for more than a year, a continuing review report needs to be submitted (within1 month of the due date i.e. 11 months from the date of approval) on or before **23/07/2023**

24/08

Dr. BARATHANE D
Member Secretary
MEMBER SECRETARY
Institutional Human Ethics Committee
MGMCRI, Puducherry - 607 402